

AN 2001:545691 CAPLUS
 DN 135:127219
 TI Preparation of pseudopolymorph of Flavopiridol
 IN Bafus, Gary L.; Harrison-Bowman, Christine M.; Silvey, Gary L.
 PA Aventis Pharmaceuticals Inc., USA
 SO PCT Int. Appl., 23 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

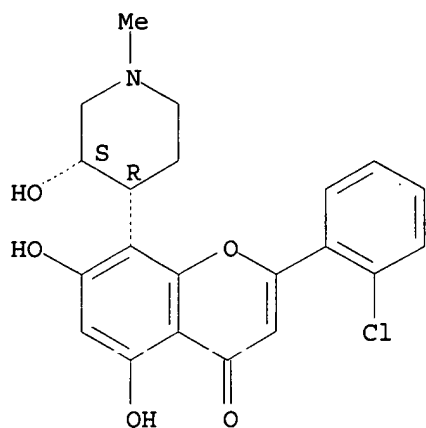
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053293	A1	20010726	WO 2001-US519	20010108
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2001007726	A	20021001	BR 2001-7726	20010108
	EP 1259507	A1	20021127	EP 2001-900939	20010108
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003520797	T2	20030708	JP 2001-553767	20010108
	NO 2002003386	A	20020912	NO 2002-3386	20020712
PRAI	US 2000-484717	A2	20000118		
	WO 2001-US519	W	20010108		
AB	Prepn. of a pseudopolymorph of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-H-1-benzopyran-4-one hydrochloride (Flavopiridol HCl, Form I), essentially free of Form II (an ethanol solvate or hydrate), a pharmaceutical compn. comprising a therapeutically effective Form I and a carrier, and methods of using the pseudopolymorph for inhibiting protein kinases are described. For example, Flavopiridol Form I was prepd. by crystn. from Form II azeotropic mixt. with ketone, i.e., Me Et ketone, and filtration of crystd. Form I.				
IT	351184-34-4P 351184-35-5P RL: PEP (Physical, engineering or chemical process); SPN (Synthetic preparation); PREP (Preparation); PROC (Process) (prepn. and compns. of pseudopolymorph of Flavopiridol as protein kinase inhibitor)				
RN	351184-34-4 CAPLUS				
CN	4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol, hydrate (9CI) (CA INDEX NAME)				

CM 1

CRN 131740-09-5

CMF C21 H20 Cl N O5 . Cl H

Absolute stereochemistry. Rotation (-).



● HCl

CM 2

CRN 64-17-5

CMF C2 H6 O

H₃C-CH₂-OH

RN 351184-35-5 CAPLUS

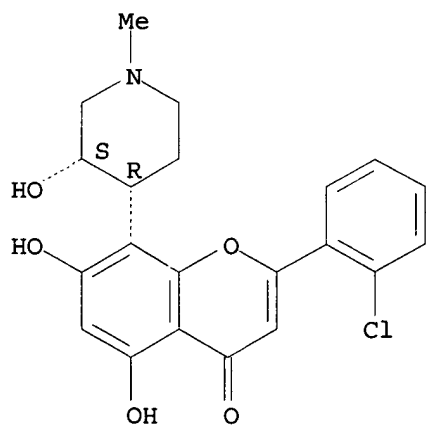
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidiny]-, compd. with 2-butanone (9CI) (CA INDEX NAME)

CM 1

CRN 146426-40-6

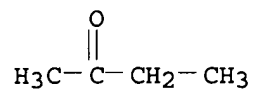
CMF C21 H20 Cl N O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 78-93-3
CMF C4 H8 O



RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 2001:545692 CAPLUS
 DN 135:127220
 TI Preparation of ethanol solvate of Flavopiridol for cancer treatment
 IN Kessler, Kurt M.
 PA Aventis Pharmaceuticals Inc., USA
 SO PCT Int. Appl., 14 pp.
 CODEN: PIXXD2

DT Patent
 LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053294	A1	20010726	WO 2001-US520	20010108
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2001007724	A	20021001	BR 2001-7724	20010108
	EP 1252155	A1	20021030	EP 2001-902993	20010108
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003520798	T2	20030708	JP 2001-553768	20010108
	US 2001051638	A1	20011213	US 2001-760590	20010116
	NO 2002003385	A	20020827	NO 2002-3385	20020712
PRAI	US 2000-487815	A2	20000118		
	US 2000-287593P	P	20000118		
	WO 2001-US520	W	20010108		
AB	An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol, Form II), a method of making Form II and a compn. comprising Form II are described. The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol as the starting compd. Since Flavopiridol is useful in treating a no. of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin-dependent kinases, including cancer, the Form II is useful for prepn. of a pharmaceutical compn. for treating cancer.				
IT	351184-37-7P RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn., properties and compns. of ethanol solvate of Flavopiridol for cancer treatment)				
RN	351184-37-7 CAPLUS				

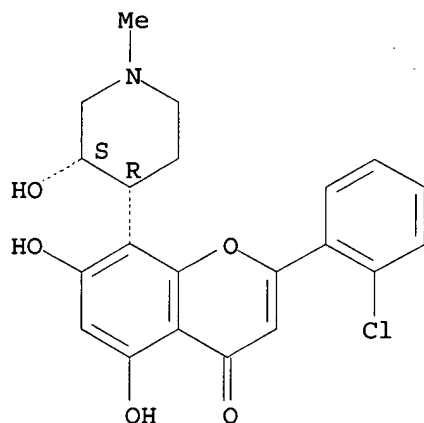
RN 351184-37-7 REGISTRY
 CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol (9CI)
 (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN Ethanol, compd. with 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4H-1-benzopyran-4-one hydrochloride (9CI)
 FS STEREOSEARCH
 MF C21 H20 Cl N O5 . x C2 H6 O . Cl H
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 131740-09-5 (146426-40-6)

CMF C21 H20 Cl N O5 . Cl H

Absolute stereochemistry. Rotation (-).



● HCl

CM 2

CRN 64-17-5

CMF C2 H6 O

H₃C-CH₂-OH

1 REFERENCES IN FILE CA (1957 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

AN 2001:434848 CAPLUS
 DN 135:51044
 TI Pharmaceutical preparation for treating tumor diseases
 IN Ghyczy, Miklos; Hager, Joerg; Wendel, Armin
 PA Rhone-Poulenc Rorer GmbH, Germany
 SO PCT Int. Appl., 34 pp.
 CODEN: PIXXD2
 DT Patent
 LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001041747	A2	20010614	WO 2000-EP11761	20001125
	WO 2001041747	A3	20020207		
	W:		AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
	RW:		GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
	DE 19959546	A1	20010621	DE 1999-19959546	19991209
	EP 1239862	A2	20020918	EP 2000-979624	20001125
	R:		AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR		
	JP 2003516348	T2	20030513	JP 2001-543092	20001125
	US 2001021704	A1	20010913	US 2000-731787	20001208
PRAI	DE 1999-19959546	A	19991209		
	WO 2000-EP11761	W	20001125		
AB	The invention relates to a pharmaceutical prepn. contg. at least one active substance that is cytostatically active, at least one biol. electron acceptor, and the customary pharmaceutical additives. The invention also relates to the use of said prepn. for treating tumor diseases, in particular, for treating cancer. Electron acceptors are betaine, phospholipids, their derivs. etc. Thus 100 g flavopiridol-HCl, 2000 g phosphatidylcholine, 40 g distearoylphosphatidylglycerol, and 250 g betaine linoleate were dispersed in 10 L ethanol; liposomes were formed. The dispersion was added to a soln. of 2 kg maltose in 2 L water, and homogenized. After filtration the dispersion was filled into vials and freeze-dried to yield 100 mg flavopiridol per vial.				

2/5/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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13932715 BIOSIS NO.: 200200561536

A high-performance liquid chromatography method using ultraviolet detection for the quantitation of flavopiridol from human plasma.

AUTHOR: Zhai Suoping; Sausville Edward; Figg William D(a)

AUTHOR ADDRESS: (a)National Cancer Institute, 9000 Rockville Pike, Building 10, Room 5A01, Bethesda, MD, 20892**USA E-Mail: wdfigg@helix.nih.gov

JOURNAL: Biomedical Chromatography 16 (6):p379-382 September, 2002

MEDIUM: print

ISSN: 0269-3879

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Flavopiridol is an inhibitor of cyclin-dependent kinase, a key regulator of cell cycle, and is currently under clinical trials. We developed and validated an HPLC assay method for the quantitation of **flavopiridol** in human plasma samples. The sample preparation consisted of protein precipitation with **acetonitrile**. Separation was accomplished on a C18 column and a C18 precolumn insert utilizing a gradient profile consisting of ammonium acetate and **methanol**. Ultraviolet detection was set at 268 nm for **flavopiridol** and 323 nm for umbelliferone, the internal standard. The method was validated over flavopiridol concentration range of 0.025-3.0 mug/mL using 250 muL of plasma. The assay was linear over this concentration range with a coefficient of variation less than 10% for inter- and intra-assay. The retention times were around 6.2 min for umbelliferone and 9.8 min for flavopiridol. The recoveries of flavopiridol and umbelliferone were 88.6 +/- 1.0% and 97.1 +/- 3.7%, respectively. This method is suitable for quantifying flavopiridol in plasma samples and further characterizing the clinical pharmacology of this compound.

REGISTRY NUMBERS: 75-05-8: ACETONITRILE; 631-61-8: AMMONIUM ACETATE;
150428-23-2: CYCLIN-DEPENDENT KINASE; 146426-40-6: FLAVOPIRIDOL;
67-56-1: METHANOL; 93-35-6: UMBELLIFERONE

=> d 1-9 sub can

L2 ANSWER 1 OF 10 REGISTRY COPYRIGHT 2002 ACS

RN 351184-35-5 REGISTRY

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, compd. with 2-butanone (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 2-Butanone, compd. with 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4H-1-benzopyran-4-one (9CI)

FS STEREOSEARCH

MF C21 H20 Cl N O5 . x C4 H8 O

SR CA

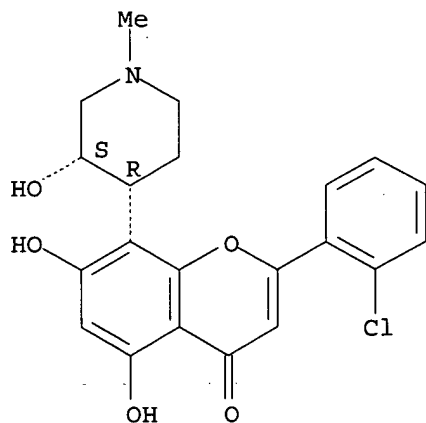
LC STN Files: CA, CAPLUS, TOXLIT

CM 1

CRN 146426-40-6

CMF C21 H20 Cl N O5

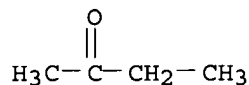
Absolute stereochemistry. Rotation (-).



CM 2

CRN 78-93-3

CMF C4 H8 O



1 REFERENCES IN FILE CA (1967 TO DATE)

1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:127219

L2 ANSWER 2 OF 10 REGISTRY COPYRIGHT 2002 ACS

RN 351184-34-4 REGISTRY

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol, hydrate (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

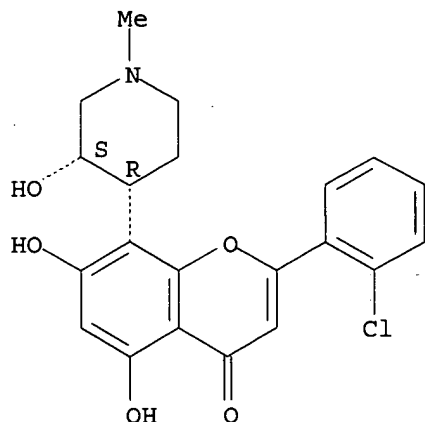
CN Ethanol, compd. with 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-

1-methyl-4-piperidinyl]-4H-1-benzopyran-4-one hydrochloride, hydrate (9CI)
FS STEREOSEARCH
MF C21 H20 Cl N O5 . x C2 H6 O . Cl H . x H2 O
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

CM 1

CRN 131740-09-5 (146426-40-6)
CMF C21 H20 Cl N O5 . Cl H

Absolute stereochemistry. Rotation (-).



● HCl

CM 2

CRN 64-17-5
CMF C2 H6 O

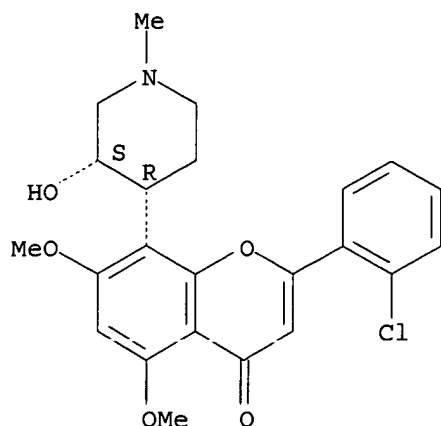
H₃C-CH₂-OH

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:127219

L2 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2002 ACS
RN 205506-16-7 REGISTRY
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-5,7-dimethoxy- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-8-(3-hydroxy-1-methyl-4-piperidinyl)-5,7-dimethoxy-, (3S-cis)-
FS STEREOSEARCH
MF C23 H24 Cl N O5
SR CA
LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER, TOXLIT, USPATFULL

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1967 TO DATE)

3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:127220

REFERENCE 2: 135:127219

REFERENCE 3: 128:270537

L2 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2002 ACS

RN 146426-40-6 REGISTRY

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, cis-(-)-

OTHER NAMES:

CN Flavopiridol

CN HMR 1275

CN L 86-8275

FS STEREOSEARCH

MF C21 H20 Cl N O5

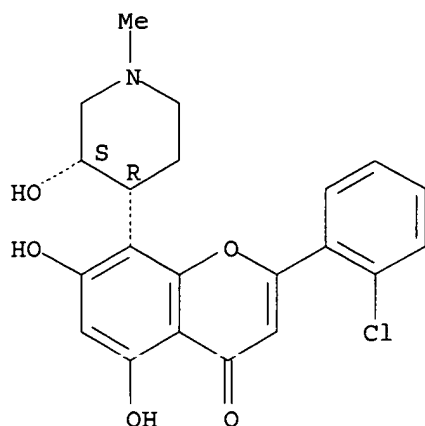
CI COM

SR CA

LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

114 REFERENCES IN FILE CA (1967 TO DATE)
 11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
 115 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:68517
 REFERENCE 2: 136:48107
 REFERENCE 3: 136:31648
 REFERENCE 4: 136:31647
 REFERENCE 5: 135:362557
 REFERENCE 6: 135:338869
 REFERENCE 7: 135:298314
 REFERENCE 8: 135:282454
 REFERENCE 9: 135:251976
 REFERENCE 10: 135:220798

L2 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2002 ACS

RN 131740-09-5 REGISTRY

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, hydrochloride, cis-(-)-

OTHER NAMES:

CN NSC 649890

FS STEREOSEARCH

MF C21 H20 Cl N O5 . Cl H

CI COM

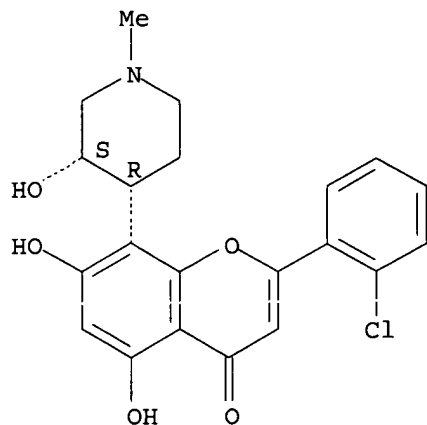
SR CA

LC STN Files: BIOSIS, CA, CAPLUS, DRUGNL, DRUGUPDATES, MRCK*, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL

(*File contains numerically searchable property data)

CRN (146426-40-6)

Absolute stereochemistry. Rotation (-).



● HCl

7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:127220
REFERENCE 2: 135:127219
REFERENCE 3: 132:329515
REFERENCE 4: 129:170064
REFERENCE 5: 128:188361
REFERENCE 6: 126:216569
REFERENCE 7: 114:61928

L2 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2002 ACS

RN 113225-21-1 REGISTRY

CN Ethanone, 1-[2-hydroxy-3-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4,6-dimethoxyphenyl]- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Ethanone, 1-[2-hydroxy-3-(3-hydroxy-1-methyl-4-piperidinyl)-4,6-dimethoxyphenyl]-, cis-(-)-

OTHER NAMES:

CN Acetoflocinipiperidol

FS STEREOSEARCH

MF C16 H23 N O5

CI COM

SR CA

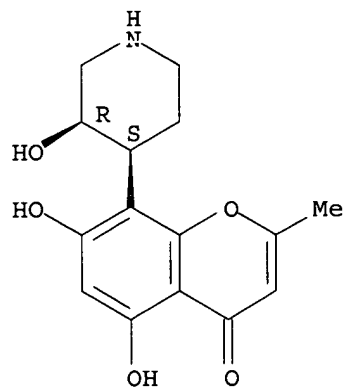
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, TOXLIT, USPATFULL

(*File contains numerically searchable property data)

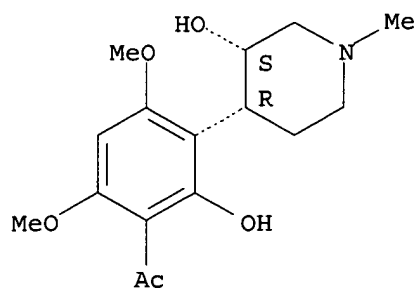
Absolute stereochemistry. Rotation (-).

L5 79 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN 4H-1-Benzopyran-4-one, 5,7-dihydroxy-8-(3-hydroxy-4-piperidinyl)-2-methyl-
, cis-(-)- (9CI)
MF C15 H17 N O5
CI COM

Rotation (-). Absolute stereochemistry unknown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:226823
REFERENCE 2: 135:127220
REFERENCE 3: 135:127219
REFERENCE 4: 134:56541
REFERENCE 5: 128:270537
REFERENCE 6: 110:8445
REFERENCE 7: 109:37739

L2 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2002 ACS

RN 113225-19-7 REGISTRY

CN 3-Piperidinol, 1-methyl-4-(2,4,6-trimethoxyphenyl)-, (3S,4R)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 3-Piperidinol, 1-methyl-4-(2,4,6-trimethoxyphenyl)-, cis-(-)-

FS STEREOSEARCH

MF C15 H23 N O4

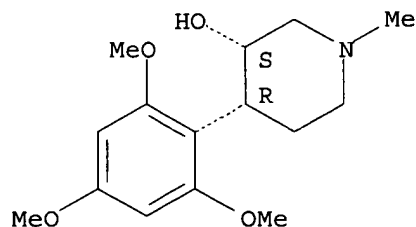
CI COM

SR CA

LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, TOXLIT, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8 REFERENCES IN FILE CA (1967 TO DATE)
8 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:127220
REFERENCE 2: 135:127219
REFERENCE 3: 134:56541
REFERENCE 4: 132:35617
REFERENCE 5: 131:129906
REFERENCE 6: 128:270537
REFERENCE 7: 110:8445
REFERENCE 8: 109:37739

L2 ANSWER 8 OF 10 REGISTRY COPYRIGHT 2002 ACS

RN 9026-43-1 REGISTRY

CN Kinase (phosphorylating), protein serine/threonine (9CI) (CA INDEX NAME)

OTHER NAMES:

CN ATP-protein transphosphorylase
CN Cytidine 3',5'-cyclic monophosphate-responsive protein kinase
CN E.C. 2.7.1.37
CN Kinase (phosphorylating), protein
CN Phosphoprotein kinase
CN Protein kinase
CN Protein kinase (phosphorylating)
CN Protein phosphokinase
CN Protein serine kinase
CN Protein serine/threonine kinase
CN Serine kinase
CN Serine protein kinase
CN Serine/threonine kinase
CN Serine/threonine phosphokinase
CN Serine/threonine protein kinase
CN Serine/threonine-specific protein kinase
CN Threonine protein kinase
DR 121855-01-4, 121855-02-5, 122007-71-0, 122544-57-4, 123057-66-9,
123175-71-3, 129430-48-4, 139074-23-0, 144999-29-1, 143515-33-7,
117056-44-7, 117277-98-2, 117590-74-6
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
CA, CABA, CAPLUS, CEN, CHEMCATS, CIN, CSCHM, EMBASE, IFICDB, IFIPAT,
IFIUDB, PROMT, TOXCENTER, TOXLIT, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

22430 REFERENCES IN FILE CA (1967 TO DATE)

62 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

22437 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:67938
REFERENCE 2: 136:66992
REFERENCE 3: 136:64972
REFERENCE 4: 136:51014
REFERENCE 5: 136:50288
REFERENCE 6: 136:37505
REFERENCE 7: 136:36358

REFERENCE 8: 136:34524

REFERENCE 9: 136:32466

REFERENCE 10: 136:32441

L2 ANSWER 9 OF 10 REGISTRY COPYRIGHT 2002 ACS

RN 610-96-8 REGISTRY

CN Benzoic acid, 2-chloro-, methyl ester (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Benzoic acid, o-chloro-, methyl ester (6CI, 7CI, 8CI)

OTHER NAMES:

CN Methyl 2-chlorobenzoate

CN Methyl o-chlorobenzoate

FS 3D CONCORD

MF C8 H7 Cl O2

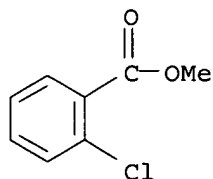
CI COM

LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST,
CSCHEM, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, SPECINFO, TOXCENTER,
TOXLIT, USPATFULL

(*File contains numerically searchable property data)

Other Sources: EINECS**, NDSL**, TSCA**

(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

132 REFERENCES IN FILE CA (1967 TO DATE)

2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

132 REFERENCES IN FILE CAPLUS (1967 TO DATE)

19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 135:195365

REFERENCE 2: 135:127220

REFERENCE 3: 135:127219

REFERENCE 4: 135:60900

REFERENCE 5: 134:366704

REFERENCE 6: 134:178321

REFERENCE 7: 134:100624

REFERENCE 8: 133:321694

REFERENCE 9: 133:309799

REFERENCE 10: 133:119881

AN 2001:545692 CAPLUS
 DN 135:127220
 TI Preparation of ethanol solvate of Flavopiridol for cancer treatment
 IN Kessler, Kurt M.
 PA Aventis Pharmaceuticals Inc., USA
 SO PCT Int. Appl., 14 pp.
 CODEN: PIXXD2

DT Patent
 LA English

FAN.CNT 1

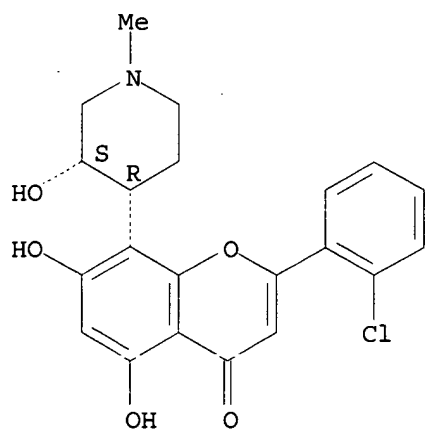
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	BR 2001007724	A	20021001	BR 2001-7724	20010108
	EP 1252155	A1	20021030	EP 2001-902993	20010108
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2001051638	A1	20011213	US 2001-760590	20010116
	NO 2002003385	A	20020827	NO 2002-3385	20020712
PRAI	US 2000-487815	A2	20000118		
	US 2000-287593P	P	20000118		
	WO 2001-US520	W	20010108		
AB	An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol, Form II), a method of making Form II and a compn. comprising Form II are described. The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol as the starting compd. Since Flavopiridol is useful in treating a no. of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin-dependent kinases, including cancer, the Form II is useful for prepn. of a pharmaceutical compn. for treating cancer.				
IT	351184-37-7P RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn., properties and compns. of ethanol solvate of Flavopiridol for cancer treatment)				
RN	351184-37-7 CAPLUS				
CN	4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol (9CI) (CA INDEX NAME)				

CM 1

CRN 131740-09-5

CMF C21 H20 Cl N O5 . Cl H

Absolute stereochemistry. Rotation (-).



● HCl

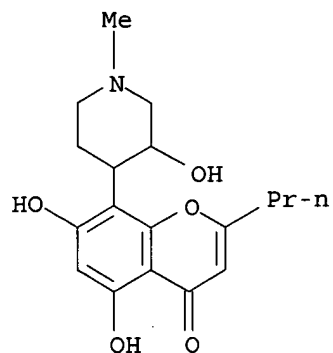
CM 2

CRN 64-17-5
CMF C2 H6 O

H₃C-CH₂-OH

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2002 ACS
RN 113225-03-9 REGISTRY
CN 4H-1-Benzopyran-4-one, 5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-2-propyl-, hydrochloride (9CI) (CA INDEX NAME)
MF C18 H23 N O5 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL



● HCl

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 109:37739

AN 2001:545692 CAPLUS
 DN 135:127220
 TI Preparation of ethanol solvate of Flavopiridol for cancer treatment
 IN Kessler, Kurt M.
 PA Aventis Pharmaceuticals Inc., USA
 SO PCT Int. Appl., 14 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053294	A1	20010726	WO 2001-US520	20010108
	W:				
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	RW:				
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	BR 2001007724	A	20021001	BR 2001-7724	20010108
	EP 1252155	A1	20021030	EP 2001-902993	20010108
	R:				
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	JP 2003520798	T2	20030708	JP 2001-553768	20010108
	US 2001051638	A1	20011213	US 2001-760590	20010116
	NO 2002003385	A	20020827	NO 2002-3385	20020712
PRAI	US 2000-487815	A2	20000118		
	US 2000-287593P	P	20000118		
	WO 2001-US520	W	20010108		

AB An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol, Form II), a method of making Form II and a compn. comprising Form II are described. The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol as the starting compd. Since Flavopiridol is useful in treating a no. of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin-dependent kinases, including cancer, the Form II is useful for prepn. of a pharmaceutical compn. for treating cancer.

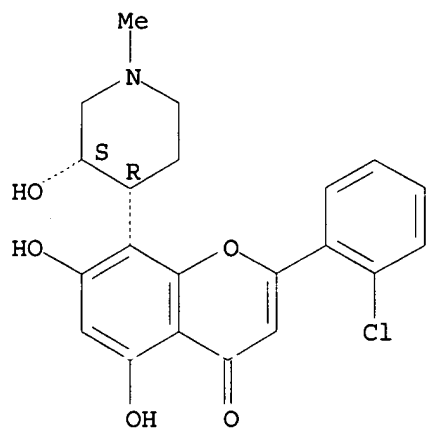
IT 351184-37-7P
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn., properties and compns. of ethanol solvate of Flavopiridol for cancer treatment)
 RN 351184-37-7 CAPLUS
 CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol (9CI)
 (CA INDEX NAME)

CM 1

CRN 131740-09-5

CMF C21 H20 Cl N O5 . Cl H

Absolute stereochemistry. Rotation (-).



● HCl

CM 2

CRN 64-17-5

CMF C2 H6 O

H₃C-CH₂-OH

RE.CNT 2

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

2/5/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

11669395 BIOSIS NO.: 199800451126

Determination of flavopiridol (L86 8275; NSC 649890) in human plasma by reversed-phase liquid chromatography with electrochemical detection.

AUTHOR: Stinson Sherman F(a); Hill Kimberly; Siford Timothy J; Phillips Lawrence R; Daw Tracy W

AUTHOR ADDRESS: (a)Lab. Drug Discovery Res. Dev., Dev. Therap. Program, Div. Cancer Treat. Diagn. Cent., Natl. Canc**USA

JOURNAL: Cancer Chemotherapy and Pharmacology 42 (4):p261-265 Sept., 1998

ISSN: 0344-5704

DOCUMENT TYPE: Article

RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Purpose: Flavopiridol is a flavone which inhibits several cyclin-dependent kinases, and exhibits potent growth-inhibitory activity against a number of human tumor cell lines both in vitro, and when grown as xenografts in mice. It is currently being evaluated in a phase I clinical trial at the National Cancer Institute. The objective of this project was to develop and validate an analytical method for the assay of flavopiridol in human plasma, with sufficient sensitivity to permit the plasma pharmacokinetics of flavopiridol to be studied during clinical trials. Methods: Flavopiridol was isolated from human plasma samples by extraction with t-butylmethyl ether following alkalization with borate buffer (pH 8.0). The extract was evaporated, the residue was dissolved in mobile phase, and analyzed by reversed-phase high-pressure liquid chromatography. Chromatography was accomplished with a polymer-based C18 column eluted with a mobile phase consisting of methanol-phosphate buffer, pH 11.0 (53:47 v/v). Electrochemical detection (ECD) was employed. Results: Flavopiridol was recovered from human plasma with an efficiency of 85-87%. Calibration curves were linear over the concentration range 10-500 nM (4.4219 ng/ml). Plasma standard concentrations were measured with an accuracy and precision ranging from 3.2% to 10%. Regression analysis of flavopiridol concentrations of 15 clinical trial plasma samples ranging in concentration from approximately 50 to 4000 muM quantitated by both ECD and mass spectrometry showed close agreement. The equation of the regression line was $y = 1.02x + 8$ with a correlation coefficient of 0.969. Continuous infusion of flavopiridol in four patients for 72 h at a rate of 50 mg/m² per day, resulted in mean steady-state plasma concentrations of from 200 to 300 nM. Levels declined in a biexponential manner following termination of the infusion, falling to approximately 10 nM after 48 h. Conclusions: An analytical method for the assay of flavopiridol in human plasma was developed with sensitivity to at least 10 nM. The assay is accurate, precise and specific, and is suitable for determination of plasma flavopiridol concentrations for pharmacokinetic studies during clinical trials.

REGISTRY NUMBERS: 146426-40-6: FLAVOPIRIDOL; 146426-40-6: L86 8275

DESCRIPTORS:

MAJOR CONCEPTS: Oncology (Human Medicine, Medical Sciences); Pharmacology

BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGANISMS: human (Hominidae)--patient

BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Animals; Chordates; Humans; Mammals; Primates; Vertebrates

DISEASES: cancer--drug treatment, neoplastic disease

CHEMICALS & BIOCHEMICALS: flavopiridol {L-86-8275}--NSC-649890, plasma level determination, antineoplastic-drug

METHODS & EQUIPMENT: reversed-phase liquid chromatography--analytical method

CONCEPT CODES:

24008 Neoplasms and Neoplastic Agents-Therapeutic Agents; Therapy
10006 Clinical Biochemistry; General Methods and Applications
13002 Metabolism-General Metabolism; Metabolic Pathways
22002 Pharmacology-General
22003 Pharmacology-Drug Metabolism; Metabolic Stimulators
22005 Pharmacology-Clinical Pharmacology (1972-)
10050 Biochemical Methods-General
10060 Biochemical Studies-General
10504 Biophysics-General Biophysical Techniques
12512 Pathology, General and Miscellaneous-Therapy (1971-)
15002 Blood, Blood-Forming Organs and Body Fluids-Blood and Lymph
 Studies

BIOSYSTEMATIC CODES:

86215 Hominidae

L10

6 L9 AND PIPERIDIN?

=> d 1-6

L10 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2002 ACS

RN 288155-43-1 REGISTRY

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3R,4R)-4-hydroxy-1-methyl-3-piperidinyl]-, rel- (9CI) (CA INDEX NAME)

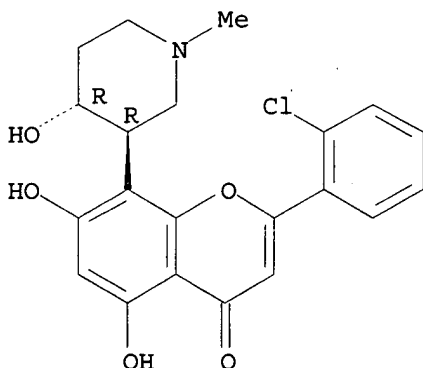
FS STEREOSEARCH

MF C21 H20 Cl N O5

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2002 ACS

RN 288155-39-5 REGISTRY

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3R,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, rel- (9CI) (CA INDEX NAME)

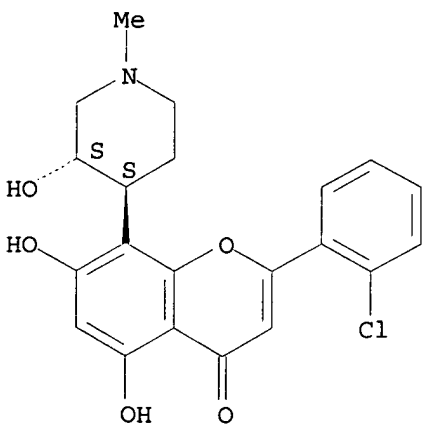
FS STEREOSEARCH

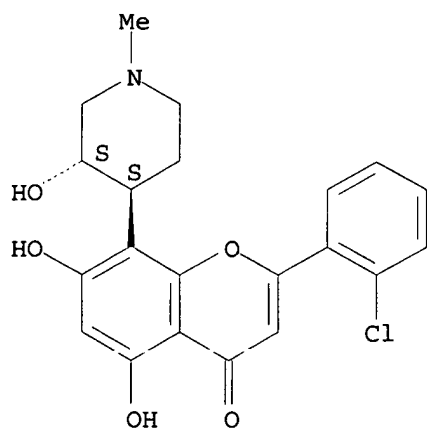
MF C21 H20 Cl N O5

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER

Relative stereochemistry.





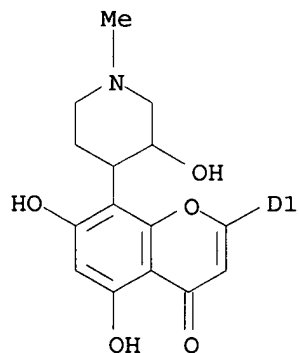
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 287397-10-8 REGISTRY
CN **4H-1-Benzopyran-4-one, 2-(chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)- (9CI)** (CA INDEX NAME)
MF **C21 H20 Cl N O5**
CI IDS
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



D1-Cl

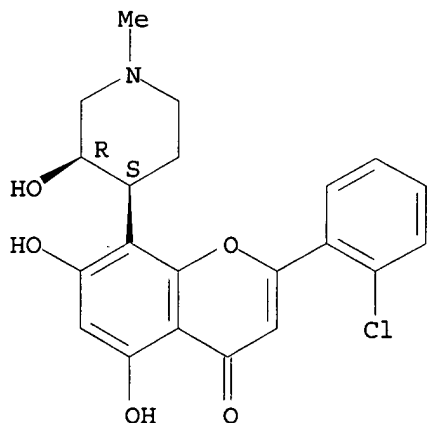


1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2002 ACS

RN 244231-67-2 REGISTRY
 CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3R,4S)-3-hydroxy-1-methyl-4-piperidinyl]-, rel- (9CI) (CA INDEX NAME)
 OTHER NAMES:
 CN (.+-.)-Flavopiridol
 CN (.+-.)-L 86-8275
 FS STEREOSEARCH
 MF C21 H20 Cl N O5
 CI COM
 SR CA
 LC STN Files: CA, CAPLUS, CASREACT, TOXCENTER

Relative stereochemistry.

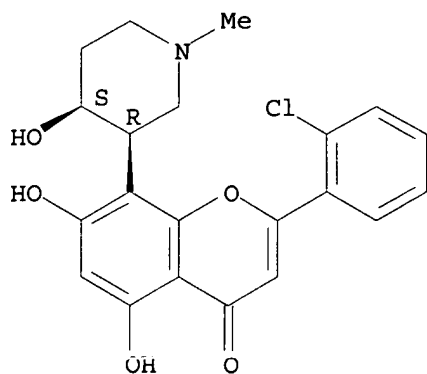


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2 REFERENCES IN FILE CA (1962 TO DATE)
 3 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2002 ACS
 RN 190972-94-2 REGISTRY
 CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3R,4S)-4-hydroxy-1-methyl-3-piperidinyl]-, rel- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(4-hydroxy-1-methyl-3-piperidinyl)-, cis-
 FS STEREOSEARCH
 MF C21 H20 Cl N O5
 SR CA
 LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1962 TO DATE)

2 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L10 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2002 ACS

RN 146426-40-6 REGISTRY

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, cis-(-)-

OTHER NAMES:

CN Flavopiridol

CN HMR 1275

CN L 86-8275

FS STEREOSEARCH

DR 358739-39-6

MF C21 H20 Cl N O5

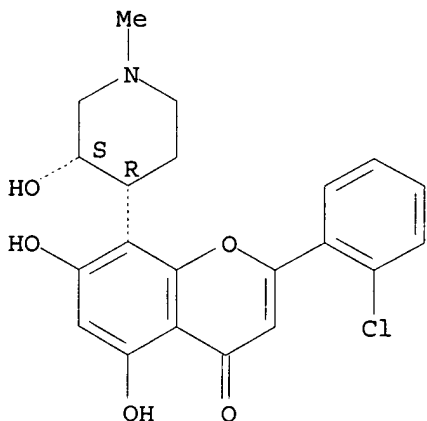
CI COM

SR CA

LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

158 REFERENCES IN FILE CA (1962 TO DATE)

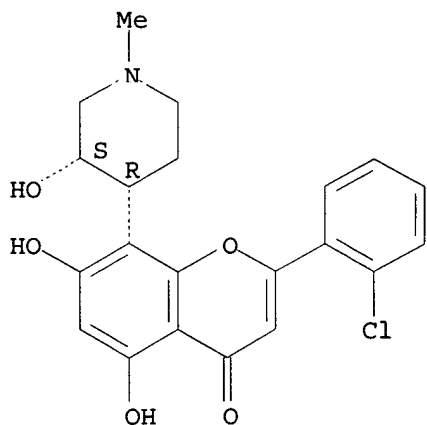
12 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

159 REFERENCES IN FILE CAPLUS (1962 TO DATE)

IN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-, hydrochloride, compd. with ethanol (9CI)
MF C21 H20 Cl N O5 . x C2 H6 O . Cl H

CM 1

Absolute stereochemistry. Rotation (-).



● HCl

CM 2

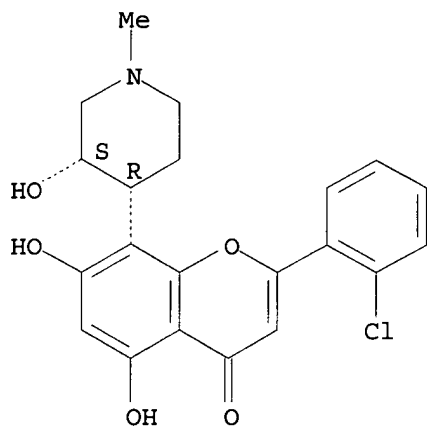
H₃C-CH₂-OH

IN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidiny]-, hydrochloride, compd. with ethanol, hydrate (9CI)

MF C21 H20 Cl N O5 . x C2 H6 O . Cl H . x H2 O

CM 1

Absolute stereochemistry. Rotation (-).



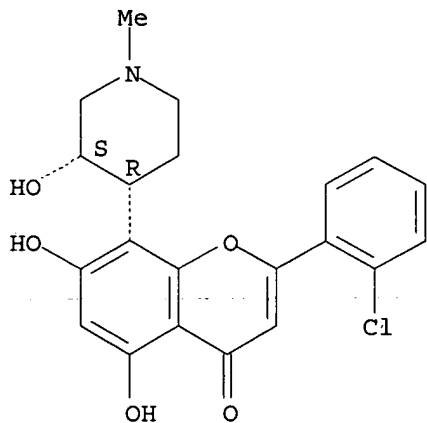
● HCl

CM 2

H₃C-CH₂-OH

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
 RN 146426-40-6 REGISTRY
 CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]- (9CI) (CA INDEX NAME)
 OTHER CA INDEX NAMES:
 CN 4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-, cis-(-)-
 OTHER NAMES:
 CN **Flavopiridol**
 CN HMR 1275
 CN L 86-8275
 FS STEREOSEARCH
 MF C21 H20 Cl N O5
 CI COM
 SR CA
 LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
 (*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



=> s 11(1)ethanol
110 L1
159899 ETHANOL
L4 2 L1(L)ETHANOL

=> d bib abs 1-2

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 2001:545692 CAPLUS
DN 135:127220
TI Preparation of ethanol solvate of Flavopiridol for cancer treatment
IN Kessler, Kurt M.
PA Aventis Pharmaceuticals Inc., USA
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053294	A1	20010726	WO 2001-US520	20010108
	W:		AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
	RW:		GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG		
	US 2001051638	A1	20011213	US 2001-760590	20010116
PRAI	US 2000-487815	A2	20000118		
	US 2000-287593	P	20000118		

AB An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol, Form II), a method of making Form II and a compn. comprising Form II are described. The Form II was prepd. using (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol as the starting compd. Since Flavopiridol is useful in treating a no. of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin-dependent kinases, including cancer, the Form II is useful for prepn. of a pharmaceutical compn. for treating cancer.

RE.CNT 2

RE

- (1) Hoechst AG; EP 0366061 A 1990 CAPLUS
- (2) Kattige, S; US 4900727 A 1990 CAPLUS

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1999:213255 CAPLUS
DN 131:35767
TI Solubilization of Ionized and Un-ionized Flavopiridol by Ethanol and Polysorbate 20
AU Li, Ping; Tabibi, S. Esmail; Yalkowsky, Samuel H.
CS Department of Pharmaceutical Sciences College of Pharmacy, University of Arizona, Tucson, AZ, 85721, USA
SO J. Pharm. Sci. (1999), 88(5), 507-509
CODEN: JPMSAE; ISSN: 0022-3549
PB American Chemical Society
DT Journal
LA English
AB Because the ionized species is more polar than its unionized counterpart, it is often assumed that the ionized species of the drug does not make a meaningful contribution to solubilization by either cosolvents or surfactants. This report extends previous studies on solubilization of

the ionic species by a combination of pH control and complexation to pH control and micellization and to pH control and cosolvency. The total aq. soly. is expressed as the addn. of the concn. of all contributing species: free un-ionized drug [Du], free ionized drug [Di], un-ionized drug micelle [DuM], and ionized drug micelle [DiM] for surfactant, and free un-ionized drug [Dcu] and free ionized drug [Dci] for cosolvent. The equations indicate that under certain conditions the ionized species can be more important in detg. the drug total soly. than the unionized species. Flavopiridol, a weak base, is used to test these newly generated equations. As expected, the micellar partition coeff. and solubilization power for ionized flavopiridol are both less than those of the un-ionized species. However, at acidic pH, the solubilities of the ionized drug in surfactant micelles [DiM] and in cosolvent-water [Dci] are both much greater than that of the unionized drug. This difference is because the solubilization of the ionized drug is proportional to its aq. soly., and its soly. [Di] can be as much as 24-fold greater than that of the free un-ionized species [Du].

RE.CNT 8

RE

- (1) Alvarez-Nunez, F; PDA J Pharm Sci Technol 1998, V52, P33 MEDLINE
- (4) Johnson, M; J Pharm Sci 1994, V83, P1142 CAPLUS
- (5) Li, P; J Pharm Sci 1998, V87, P1535 CAPLUS
- (7) Okimoto, K; Pharm Res 1996, V13, P256 CAPLUS
- (8) Tinwalla, A; Pharm Res 1993, V10, P1136 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s 11/p

L13 9 L1/P

=> d bib abs 1-9

L13 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 2001:545692 CAPLUS

DN 135:127220

TI Preparation of ethanol solvate of Flavopiridol for cancer treatment
IN Kessler, Kurt M.

PA Aventis Pharmaceuticals Inc., USA

SO PCT Int. Appl., 14 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053294	A1	20010726	WO 2001-US520	20010108
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	US 2001051638	A1	20011213	US 2001-760590	20010116
PRAI	US 2000-487815	A2	20000118		
	US 2000-287593	P	20000118		

AB An ethanol solvate form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one (Flavopiridol, Form II), a method of making Form II and a compn. comprising Form II are described. The Form II was prep'd. using (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol as the starting comp'd. Since Flavopiridol is useful in treating a no. of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin-dependent kinases, including cancer, the Form II is useful for prepn. of a pharmaceutical compn. for treating cancer.

RE.CNT 2

RE

(1) Hoechst AG; EP 0366061 A 1990 CAPLUS

(2) Kattige, S; US 4900727 A 1990 CAPLUS

L13 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 2001:545691 CAPLUS

DN 135:127219

TI Preparation of pseudopolymorph of Flavopiridol

IN Bafus, Gary L.; Harrison-Bowman, Christine M.; Silvey, Gary L.

PA Aventis Pharmaceuticals Inc., USA

SO PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001053293	A1	20010726	WO 2001-US519	20010108
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,			

SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-484717 A2 20000118

AB Prepn. of a pseudopolymorph of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-H-1-benzopyran-4-one hydrochloride (Flavopiridol HCl, Form I), essentially free of Form II (an ethanol solvate or hydrate), a pharmaceutical compn. comprising a therapeutically effective Form I and a carrier, and methods of using the pseudopolymorph for inhibiting protein kinases are described. For example, Flavopiridol Form I was prepd. by crystn. from Form II azeotropic mixt. with ketone, i.e., Me Et ketone, and filtration of crystd. Form I.

RE.CNT 3

RE

(1) Li, P; PDA J Pharm Sci Technol 1999, V53(3), P137 CAPLUS

(2) Naik, R; US 5284856 A 1994 CAPLUS

(3) Sedlacek; Int J Oncology V9, P1143 CAPLUS

L13 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 2001:283821 CAPLUS

DN 134:316086

TI Manufacture of polyglutamate-therapeutic agent conjugates

IN Kumar, Anil M.; Klein, J. Peter; Bhatt, Rama; Vawter, Edward

PA Cell Therapeutics, Inc., USA

SO PCT Int. Appl., 44 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026693	A2	20010419	WO 2000-US28109	20001012
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRAI US 1999-159135 P 19991012

AB The invention provides new processes for prepg. polyglutamic acid-therapeutic agent conjugates for clin. development and pharmaceutical use, and polyglutamic acid-therapeutic agent conjugates prepd. by these processes. Poly(L-glutamic acid) in N,N-dimethylformamide was reacted with paclitaxel in presence of N,N-diisopropylcarbodiimide to obtain poly-L-glutamic acid-2'-paclitaxel conjugate.

L13 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 2001:128852 CAPLUS

DN 134:366704

TI A stereocontrolled approach to substituted piperidones and piperidines: flavopiridol D-ring analogs

AU Gross, A.; Borcharding, D. R.; Friedrich, D.; Sabol, J. S.

CS Aventis Pharmaceuticals Inc., Bridgewater, NJ, 08807-0800, USA

SO Tetrahedron Lett. (2001), 42(9), 1631-1633

CODEN: TELEAY; ISSN: 0040-4039

PB Elsevier Science Ltd.

DT Journal

LA English

AB A stereocontrolled approach to substituted piperidones and piperidines is

presented, and their utility as intermediates for the synthesis of flavopiridol D-ring analogs is described.

RE.CNT 7

RE

- (1) Gonzalez, F; Org Synth 1986, V64, P175 CAPLUS
- (2) Johnson, W; J Am Chem Soc 1970, V92, P741 CAPLUS
- (3) Kattige, S; US 4900727 1990 CAPLUS
- (4) Naik, R; US 5284856 1988 CAPLUS
- (5) Naik, R; Tetrahedron 1988, V44, P2081 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 2000:727121 CAPLUS

DN 134:56541

TI Thio- and Oxoflavopiridols, Cyclin-Dependent Kinase 1-Selective Inhibitors: Synthesis and Biological Effects

AU Kim, Kyoung Soon; Sack, John S.; Tokarski, John S.; Qian, Ligang; Chao, Sam T.; Leith, Leslie; Kelly, Yolanda F.; Misra, Raj N.; Hunt, John T.; Kimball, S. David; Humphreys, William G.; Wautlet, Barris S.; Mulheron, Janet G.; Webster, Kevin R.

CS Departments of Oncology Chemistry Oncology Drug Discovery Structural Biology and Modelling and Metabolism and Pharmacokinetics, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA

SO J. Med. Chem. (2000), 43(22), 4126-4134

CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

OS CASREACT 134:56541

AB Flavopiridol analogs, thio- and oxoflavopiridols which contain a sulfur or oxygen atom linker between a chromone ring and the hydrophobic side chain, are selective cyclin-dependent kinase 1 (CDK1) inhibitors with an IC50 of 110 and 130 nM. Dynamic kinetic resolu. of the racemate gave the intermediate (+)-(R)-1-methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinone which was reduced to give (3S,4R)-1-methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinol. One of the target compds. thus prepd. was (-)-2-[(2-chlorophenyl)thio]-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4H-1-benzopyran-4-one hydrochloride. Hydrophobic side chains such as chlorophenyl or tert-Bu produced potent CDK1 inhibitory activity, while hydrophilic side chains such as pyrimidine or aniline caused a severe redn. in CDK inhibitory activity. These analogs are competitive inhibitors with respect to ATP, and therefore activity was dependent upon the CDK subunit without being affected by the cyclin subunit or protein substrate. Some thio- and oxoflavopiridols are not only selective within the CDK family but also discriminated between unrelated serine/threonine and tyrosine protein kinases. CDK1 selective thio- and oxoflavopiridol analogs inhibit the colony-forming ability of multiple human tumor cell lines and possess a unique antiproliferative profile in comparison to flavopiridol.

RE.CNT 41

RE

- (1) Abraham, R; Biol Cell 1995, V83, P105 CAPLUS
- (2) Bairoch, A; Nucleic Acids Res 2000, V28, P45 CAPLUS
- (4) Burley, S; FEBS Lett 1986, V203, P139 CAPLUS
- (5) Carlson, B; Cancer Res 1996, V56, P2973 CAPLUS
- (6) de Azevedo, W; Proc Natl Acad Sci U S A 1996, V93, P2735 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 1998:494641 CAPLUS

DN 129:227384

TI Exploiting chemical libraries, structure, and genomics in the search for kinase inhibitors

AU Gray, Nathanael S.; Wodicka, Lisa; Thunnissen, Andy-Mark W. H.; Norman,

Thea C.; Kwon, Soojin; Espinoza, F. Hernan; Morgan, David O.; Barnes, Georjana; LeClerc, Sophie; Meijer, Laurent; Kim, Sung-Hou; Lockhart, David J.; Schultz, Peter G.

CS Howard Hughes Med. Inst., Univ. California, Berkeley, CA, 94720, USA

SO Science (Washington, D. C.) (1998), 281(5376), 533-538

CODEN: SCIEAS; ISSN: 0036-8075

PB American Association for the Advancement of Science

DT Journal

LA English

AB Selective protein kinase inhibitors were developed on the basis of the unexpected binding mode of 2,6,9-trisubstituted purines to the ATP-binding site of the human cyclin-dependent kinase 2 (CDK2). By iterating chem. library synthesis and biol. screening, potent inhibitors of the human CDK2-cyclin A kinase complex and of *Saccharomyces cerevisiae* Cdc28p were identified. The structural basis for the binding affinity and selectivity was detd. by anal. of a three-dimensional crystal structure of a CDK2-inhibitor complex. The cellular effects of these compds. were characterized in mammalian cells and yeast. In the latter case the effects were characterized on a genome-wide scale by monitoring changes in mRNA levels in treated cells with high-d. oligonucleotide probe arrays. Purine libraries could provide useful tools for analyzing a variety of signaling and regulatory pathways and may led to the development of new therapeutics.

L13 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 1998:208527 CAPLUS

DN 128:270537

TI Process for the preparation of chiral ketones as intermediates for flavopiridol and analogs

IN Kim, Kyoung Soon

PA Bristol-Myers Squibb Co., USA

SO PCT Int. Appl., 22 pp.

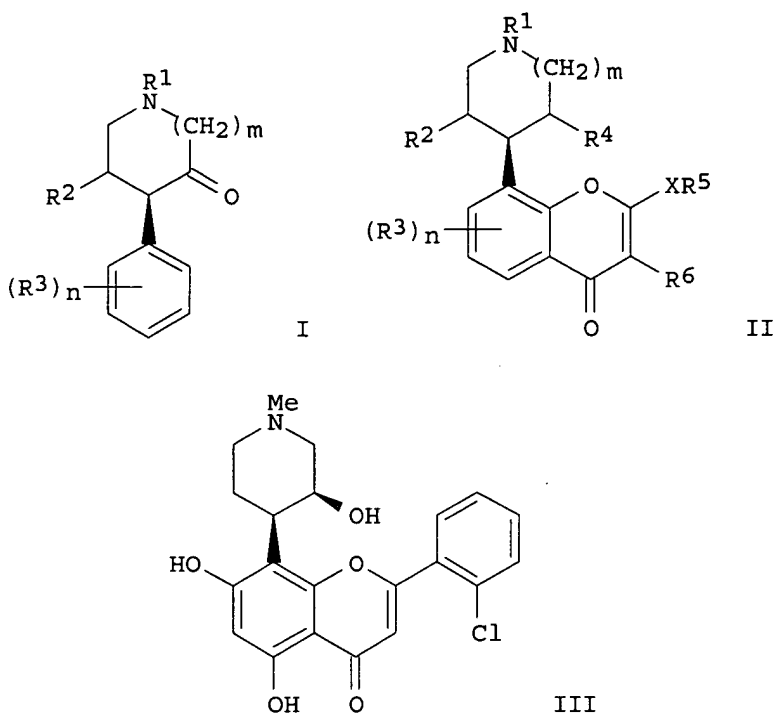
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9813344	A1	19980402	WO 1997-US16432	19970916
	W:	AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
	US 5908934	A	19990601	US 1997-927609	19970912
	AU 9743517	A1	19980417	AU 1997-43517	19970916
PRAI	US 1996-26748		19960926		
	WO 1997-US16432		19970916		
OS	CASREACT 128:270537; MARPAT 128:270537				
GI					



AB A process for prepg. chiral phenylpiperidones [I; R1 = H, (cyclo)alkyl, aryl(alkyl), alkylcarbonyl, (CH2)_qNR7R8, etc.; R2 = H, OH, halo, alkoxy, carboxy, (cyclo)alkyl, aryl(alkyl), alkylcarbonyloxy, alkylthio, NR7R8, etc.; R3 = H, OH, alkoxy, (cyclo)alkyl, aryl(alkyl), aryloxy, CHO, etc.; R7, R8 = H, (cyclo)alkyl, aryl(alkyl), heterocyclyl, etc.; R7R8N may form a hetero ring; m = 0-2; n = 1-3; q = 2-5] and piperidinylbenzopyranones [II; R1-R3, m, n, q as above; R4 = H, OH, alkoxy, (cyclo)alkyl, aryl(alkyl), amino, thiol, etc.; R5 = (cyclo)alkyl, aryl(alkyl), heterocyclyl(alkyl); R6 = H, OH, halo, alkyl, aryl(alkyl), NO2, amino, etc.; X = bond, O, S] and their pharmaceutically acceptable salts is claimed, comprising (a) salification of a racemic I with a chiral acid in an org. solvent and (b) treatment of the salt with an aq. base. Compds. I are useful as intermediates in the prepn. of protein kinase inhibitors. Thus, a mixt. of 1.60 g (.-.-)-1-methyl-4-(2,4,6-trimethoxyphenyl)-3-piperidinone and 2.28 g dibenzoyl-D-tartaric acid in 10 mL MeOH was heated at reflux under Ar and stirred overnight at the ambient temp. to give 2.89 g salt which was dissolved in a mixt. of 40 mL CH2Cl2 and 12 mL 0.5 N aq. NaOH, the org. phase was sepd. and worked up to give 1.60 g (R)-piperidone I (R1 = Me, R2 = H, (R3)₃ = 2-, 4- and 6-MeO, m = 1) [m. 131-133, [.alpha.D] = +31.degree. (MeOH, c 1.0)]. This was subjected to redn. with (Me2CHCH2)2AlH, the resulting 3-piperidinol intermediate C-acetylated and partially demethylated with Ac2O and BF3.cntdot.THF in CH2Cl2 to give (3S-cis)-4-(3-acetyl-2-hydroxy-4,6-dimethoxyphenyl)-1-methyl-3-piperidinol which was cyclocondensed with Me 2-chlorobenzoate in presence of NaH in DMF and the resulting 2-(2-chlorophenyl)benzopyranone subjected to MeO ether cleavage with BBr3 in ClCH2CH2Cl to give cis-piperidinylbenzopyranone III.

L13 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 1997:752833 CAPLUS

DN 128:34632

TI Preparation of 2-thia- or 2-oxa-flavopiridol analogs for use as protein kinase inhibitors

IN Kim, Kyoung Soon

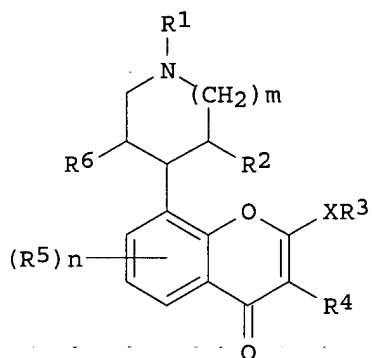
PA Bristol-Myers Squibb Company, USA

SO PCT Int. Appl., 46 pp.

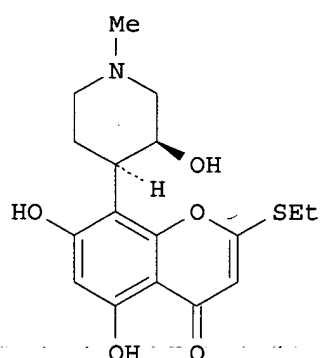
CODEN: PIXXD2

DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9742949	A1	19971120	WO 1997-US7610	19970506
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9730594	A1	19971205	AU 1997-30594	19970506
PRAI	US 1996-17529		19960510		
	WO 1997-US7610		19970506		
OS	MARPAT 128:34632				
GI					



I



II

AB Flavopiridol analogs I [X = S, O; R1 = H, alkyl, aryl, cycloalkyl, acyl, alkoxy, carbonyl, aryloxy, carbonyl; R2 = R6 = H, OH, SH, alkyl, aryl, cycloalkyl, alkoxy, aryloxy, alkoxy, carbonyl, aryloxy, carbonyl, amino, alkylthio, arylthio; R3 = alkyl, cycloalkyl, aryl, heterocyclyl; R4 = H, NO2, OH, alkyl, aryl, amino, halogen, alkoxy, carboxy, heterocyclyl, alkoxy, carbonyl; R5 = H, OH, CHO, CN, NO2, halogen, alkyl, aryl, cycloalkyl, alkoxy, aryloxy, alkyl, carbonyloxy, aryl, carbonyloxy, carboxy, amino, alkylthio, alkyl, sulfinyl, carbamoyloxy; m = 0 - 3; n = 0 - 3] were prepd. for use as protein kinase inhibitors which are useful in the treatment of proliferative diseases, such as cancer, inflammation, or arthritis. Thus, II was prepd. starting from 1,3,5-trimethoxybenzene and 1-methyl-2-piperidone. The prepd. compds. were tested for cdk4/cyclin D1 kinase inhibition.

L13 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2001 ACS

AN 1995:826475 CAPLUS

DN 123:228772

TI Preparation of prodrugs for enzyme-mediated activation

IN Bosslet, Klaus; Czac, Joerg; Hoffmann, Dieter; Tillequin, Francois; Florent, Jean-Claude; Azoulay, Michel; Monneret, Claude; Jacquesy, Jean-Claude; Gesson, Jean-Pierre; Et, Al.

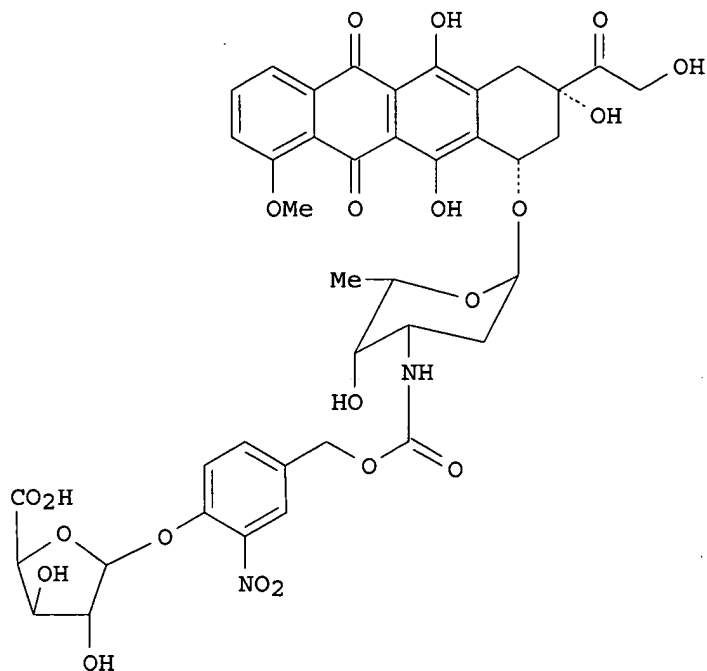
PA Behringwerke Aktiengesellschaft, Germany; Laboratories Hoechst S.A.

SO Eur. Pat. Appl., 14 pp.

CODEN: EPXXDW

DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 642799	A1	19950315	EP 1994-113388	19940826
	EP 642799	B1	20011107		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	EP 647450	A1	19950412	EP 1993-114475	19930909
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	AU 9471699	A1	19950323	AU 1994-71699	19940907
	AU 678494	B2	19970529		
	CA 2131662	AA	19950310	CA 1994-2131662	19940908
	NO 9403319	A	19950310	NO 1994-3319	19940908
	ZA 9406920	A	19950412	ZA 1994-6920	19940908
	JP 07149667	A2	19950613	JP 1994-214597	19940908
	US 5621002	A	19970415	US 1994-302459	19940909
PRAI	EP 1993-114475	A	19930909		
	DE 1992-4236237		19921027		
OS	MARPAT 123:228772				
GI					



I

AB Enzymically cleavable prodrugs SZW (S = modified competitive enzyme inhibitor; W = pharmacol. active substance; Z = bond, self-immolative spacer group; such that the Z-S bond can be enzymically cleaved at a ≈ 2 -fold lower Michaelis-Menten const.) (e.g., I), with reduced Michaelis-Menten consts., are prepd.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
26 July 2001 (26.07.2001)

PCT

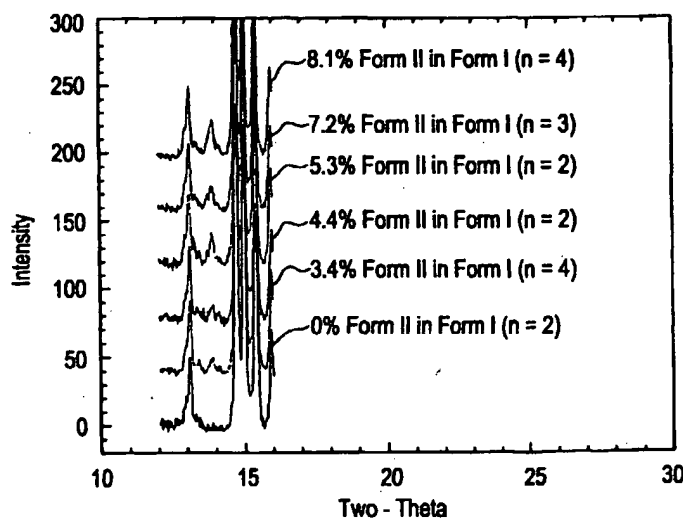
(10) International Publication Number
WO 01/53293 A1

- (51) International Patent Classification: C07D 405/04, A61K 31/435, A61P 35/00
- (21) International Application Number: PCT/US01/00519
- (22) International Filing Date: 8 January 2001 (08.01.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/484,717 18 January 2000 (18.01.2000) US
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 09/484,717 (CIP)
Filed on 18 January 2000 (18.01.2000)
- (71) Applicant (for all designated States except US): AVENTIS PHARMACEUTICALS INC. [US/US]; Mail Stop EMC-G1, Route 202-206; P.O. Box 6800, Bridgewater, NJ 08807-0800 (US).
- (72) Inventors; and
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[Continued on next page]

(54) Title: PSEUDOPOLYMORPH OF (-)-CIS-2-(2-CHLOROPHENYL)-5,7-DIHYDROXY-8[4R-(3S-HYDROXY-1-METHYL)PIPERIDINYL]-4H-1-BENZOPYRAN-4-ONE

Estimated Detection Limit
HMR 1275 Form II in Form I Bulk Drug Substance



(57) Abstract: The present invention comprises a pseudopolymorph of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, a method of making same, a pharmaceutical composition and methods of using the pseudopolymorph.

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Ps udop lymorph of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one

5

BACKGROUND OF THE INVENTION

The compound (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one or one of its pharmaceutically acceptable salt forms (known as "Flavopiridol") is an immunomodulator and antiinflammatory agent (U. S. Patent no. 4,900,727), and inhibitor of oncogene-encoded kinases or growth factor receptor tyrosine kinases (US Patent no. 5,284,856). Flavopiridol is a strong inhibitor of cyclin dependent kinases (CDKs) including CDK1, CDK2, CDK4, CDK6 and CDK7, (cdk1/cyclin B; cdk2/cyclin A; cdk2/cyclin E; cdk4/cyclinD; cdk6/cyclinD; cdk7/cyclin H) with the potential to cause inhibition of cell cycle progression in G₁ and G₂ by multiple mechanisms relatable to cdk inhibition. See *International Journal of Oncology* 9: 1143-1168 (1996). Also, Flavopiridol has been shown to inhibit the EGF receptor family, the receptor associated SRC family kinases, and signal transducing kinases. In vitro and in vivo experiments have shown that Flavopiridol is able to inhibit a broad type range of human tumors, leukemias and lymphomas.

(-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one or a pharmaceutically acceptable salt thereof crystallizes into numerous solvates with solvents such as ethanol, DMSO, methanol, acetonitrile/isopropanol, ethanol/isopropanol, and isopropanol and solvate hydrates such as ethanol/ and isopropanol/water combinations. The preferred form is the Flavopiridol hydrochloride ethanol/water solvate form (hereafter "Form II").

Although Form II meets pharmaceutical standards, it has a tendency to absorb water if not packaged in water impermeable packaging, which increases cost of production. It is also desirable to have as much stability as possible in the crystalline structure for handling purposes and for approvals through different pharmaceutical regulatory agencies throughout the world.

It is an object of the present invention to provide a form of Flavopiridol as Form I which has superior physical characteristics for use as a pharmaceutical composition.

SUMMARY OF THE INVENTION

5 The present invention comprises pseudopolymorph Form I as defined by x-ray powder diffraction. Preferably, Form I is essentially free of Form II and/or other Flavopiridol forms. It is useful in a pharmaceutical composition comprising an effective amount of Form I and a pharmaceutically acceptable carrier. Form I is useful as a protein kinase inhibitor, cyclin dependent kinase inhibitor, and in the
10 treatment for various forms of cancer.

Form I is further characterized by its ability of being less hygroscopic than Form II e.g., has less weight gain due in comparative relative humidities.

15 Form I is prepared by combining a sufficient quantity of Form II with a sufficient amount of an appropriate azeotropic solvent thus forming an azeotropic mixture; submitting the azeotropic mixture to azeotropic distillation sufficient to form Form I; and optionally recovering Form I therefrom.

DESCRIPTION OF DRAWING

20 Figure 1: Estimated Limit of Detection of Form II in Form I by X-ray Powder Diffraction (XRPD)

25 To estimate the limit of detection of Form II in Form I, varying quantities of Form II were accurately weighed and carefully mixed (unmilled) with Form I. The entire mixture was transferred to a platinum sample holder and leveled using glass microscope slide. All samples were scanned at 0.2°/min. from 12° - 16° 2 θ . At a minimum, duplicate determinations were made at each spike level, the XRPD
30 patterns averaged, and the peak height at ~13.8° 2 θ measured to the nearest 0.1 mm. The estimated detection limit of Form II in Form I is ~ 3%.

DETAILED DESCRIPTION OF THE INVENTION

"Form I" means (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidiny]-4H-1-benzopyran-4-one hydrochloride. It has the same active ingredient as Flavopiridol but differs from known crystals of Flavopiridol in that it is anhydrous and/or solvate free, i.e., a pseudopolymorph of known forms of Flavopiridol.

Form I is identified by x-ray diffraction patterns expressed in terms of "d" spacing using Cu K-alpha radiation as follows:

10	D space- Å
	12.708
	4.323
	5.594
	5.349
15	3.590,

and more preferably as:

	D space- Å
	12.708
	4.323
20	5.594
	5.349
	3.590
	3.366
	4.209
25	3.395
	3.438
	4.839.

Also, Form I is identified by x-ray diffraction patterns expressed in terms of "d" spacing using Cu K-alpha radiation and the Relative Intensities thereof:

	D space- Å	Relative Intensities
	12.708	Strong
	4.323	Strong
	5.594	Strong
35	5.349	Medium
	3.590	Medium
	3.366	Medium
	4.209	Medium
	3.395	Medium
40	3.438	Medium
	4.839	Medium.

More preferably, Form I is identified x-ray diffraction patterns expressed in terms of "d" spacing using Cu K-alpha radiation and the Relative Intensities (RI) percentages thereof:

D space- Å	Relative Intensity %
12.708	100.0
4.323	75.9
5.594	58.5
5.349	49.5
3.590	46.6
3.366	42.0
4.209	40.7
3.395	39.5
3.438	38.8
4.839	37.1

Form I X-ray powder diffraction is more fully described in Table 1.

Table 1

2 Theta Angle (°)	D Space - Å	Relative Intensity	Relative Intensity (%)
6.950	12.708	Strong	100.0
20.529	4.323	Strong	75.9
15.830	5.594	Strong	58.5
16.560	5.349	Medium	49.5
24.778	3.590	Medium	46.6
26.457	3.366	Medium	42.0
21.091	4.209	Medium	40.7
26.226	3.395	Medium	39.5
25.898	3.438	Medium	38.8
18.320	4.839	Medium	37.1
8.308	10.634	Medium	35.7
23.748	3.744	Medium	33.4
13.010	6.799	Medium	32.4
30.520	2.927	Medium	31.0
27.106	3.287	Weak	26.2
31.153	2.869	Weak	22.4
29.043	3.072	Weak	23.7
14.600	6.062	Weak	22.4
19.033	4.659	Weak	20.6

Form I is preferably essentially free of Form II and/or other forms of Flavopiridol. "Essentially free" of Form II and/or other forms of Flavopiridol means

that Form II and/or other forms of Flavopiridol are present in less than 10%, 9%, 8%, 7%, 6%, 5%, 4% and 3% as shown by x-ray powder diffraction or Nuclear Magnetic Resonance (NMR).

5 "Other forms of Flavopiridol" include base and salt forms as is appropriate, and which include hydrates, solvates or solvate hydrates, but does not include Form I or Form II.

10 "Form II" means the solvate/hydrate of ethanol/water of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidiny]-4H-1-benzopyran-4-one hydrochloride as described by x-ray powder diffraction in Table 2, obtained using Cu K-alpha radiation.

Table 2

2 Theta Angle (°)	D Space- Å	Relative Intensity (%)
6.920	12.763	100.0
13.850	6.389	35.7
27.908	3.194	22.2
6.669	13.244	18.0
20.838	4.259	13.8
7.339	12.036	13.8
31.660	2.824	9.5
10.208	8.659	8.3
14.722	6.012	7.2
16.413	5.397	6.9
25.829	3.447	6.5

15 Preferably, Form I is made by combining a sufficient quantity of Form II with a sufficient amount of an appropriate azeotropic solvent to form an azeotropic mixture; submitting the azeotropic mixture to azeotropic distillation sufficient to form Form I; and optionally recovering Form I.

20 A "sufficient quantity of Form II" is an amount to form crystals of Form I in the reaction mixture which can be recovered. One skilled in the art may experimentally determine this quantity.

A "sufficient quantity of a suitable solvent" is enough suitable solvent to at least partially dissolve Form II thus forming a reaction mixture and can be experimentally determined by one skilled in the art. The experiments described hereafter give examples of quantities that could be used.

5

"Appropriate conditions" in large part depend upon the suitable solvent selected. For example, if the appropriate conditions comprise azeotropic distillation, an appropriate azeotropic solvent will be selected.

10

A "suitable solvent" is a solvent that at least partially dissolves Form II, and permits the formation of crystals of Form I. The suitable solvent can be an "appropriate azeotropic solvent" or as otherwise described herein.

15

"Azeotropic mixture" refers to a liquid mixture of two or more substances which behaves like a single substance in that the vapor produced by partial evaporation of liquid has the same composition as the liquid. The constant boiling mixture exhibits either a maximum or minimum boiling point as compared with that of other mixtures of the same substance.

20

"Azeotropic distillation" refers to a type of distillation in which a substance is added to the mixture to be separated in order to form an azeotropic mixture with one or more of the constituents of the original mixture. Typically, the azeotropic mixture is heated to a temperature at which the solvate/water is driven off of Form II. The azeotropes thus formed will have boiling points different from the boiling

25

"Appropriate azeotropic solvent"(s), comprise ketone solvents such as acetone, methyl ethyl ketone and the like; aliphatic ester solvents such as ethyl acetate, methyl acetate, methyl formate, ethyl formate, isopropyl acetate and the like; mixtures of ketone solvents and aliphatic ester solvents; C₅-C₈ aliphatic solvents such as pentane, hexane and the like; aliphatic nitriles, such as acetonitrile; benzene, toluene, pyridine, and so on. See for example Practical Organic Chemistry, 3rd ed., John Wiley & Sons, 1956 e.g., pp. 10-11, incorporated herein by reference.

30

As used herein, the term "suitable temperature" refers to that temperature which is permit the crystallization of Form I without substantial damage to the Form I thus formed. In the azeotropic distillation, it will be the boiling point at which the
5 solvate and/or water has been driven off.

At this point, the Form I is in the form of a crystal which has precipitated and which may be recovered by isolating the crystal. Typically, this may be accomplished by filtering the crystal or evaporating the solvent or otherwise removing the solvent
10 from the crystal, or the crystal from the solvent. Drying of the solvent, e.g. evaporation at ambient temperature or upon heating, may also be appropriate.

An important feature of Form I over Form II is the ability of Form I not to absorb
15 water readily from the atmosphere. The present invention provides a form of Flavopiridol which has a weight gain due to water of less than 5%, including 4%, 3%, 2%, 1% and less than 1% in fractions (normally about 1-2%) with a Relative Humidity of about 75% and even up to a Relative Humidity of about 90% (weight gain of about 3.5%). Form II, as a solvate/hydrate, showed a slow but continual weight gain of
20 about 4% through about 60% Relative Humidity. Above 60%, Form II showed a weight gain of about 15-20%.

EXAMPLE 1

Preparation of Flavopiridol Form I

25 Approximately 6 g of Flavopiridol Form II was placed in a 600 mL beaker. 300 mL of Methyl ethyl ketone (MEK) was added slowly, with stirring, to obtain a slurry. The solution was heated slowly to 50°C until cloudy. The temperature was increased to about 73°C with stirring and the addition of 100 ml of solvent. As the solution was brought to a strong boil it began to precipitate out and settle to the bottom. The
30 temperature was increased and monitored to 80°C (boiling point of MEK), for a few minutes to obtain additional precipitate, then removed and allowed to cool to about 55°C. The final volume of 325 mL of solution required filtering through a Buchner funnel, under vacuum, using Whatman #1 filter paper, until dry; resulting in a dense yellow and flocculent chunk-like powder. The structure was confirmed by Mass

Spectrometry, Nuclear Magnetic Resonance and Fourier Transform Infra Red, and X-Ray powder diffraction performed on the sample.

EXAMPLE 2

X-Ray Powder Diffraction Methodology

X-ray powder diffraction (XRPD) patterns were obtained on a Scintag XDS
5 2000 θ/θ diffractometer operating with copper radiation at 45kV and 40mA, using a
Kevex Psi Peltier-cooled silicon detector. The source slits of 2 and 4 mm, and
detector slits of 0.5 and 0.3 mm were used for data collection. Sample obtained was
gently milled using an agate mortar and pestle for approximately one minute, placed
in a platinum sample holder, and leveled using a glass microscope slide. Powder
10 diffraction patterns of the samples were obtained from 2° to 42° 2θ at $1^\circ/\text{min}$.
Calibration of the XDS 2000 is verified annually using a silicon powder standard.

EXAMPLE 3

Hygroscopicity screening - Comparison of Form I and Form II

15 Dynamic Vapor Sorption (DVS) analysis studies were conducted on Form II versus
Form I.

Dynamic Water Vapor Sorption Analysis (DVS)

Form II was studied at 25°C using a Surface Measurement Systems Dynamic
Vapor Sorption DVS-1 analyzer. A sample in the range of about 14.8 mg was placed
20 in a tared quartz sample holder at an initial ambient room humidity setting of about
48% Relative Humidity (RH). A total wet/dry nitrogen flow rate of 200 cc/min was
used throughout the study. The following full cycle program was initiated: 30 min at
the initial ambient RH, followed by settings of 0, 20, 40, 60, 80, 90, 95 and 98%RH,
with exposure time at each humidity set point dependent upon dm/dt being less than
25 0.001% for 60 min. The maximum time allowed at any one humidity set point was 24
hours. For a full cycle, data collection took about 4 days to complete. After the full
cycle the sample was maintained at the same RH as the initial ambient starting RH.

Form I was studied at 25°C and 40°C using the DVS-1 analyzer. Data was
30 collected over two full cycles. Samples of 10.4 and 16.7 mg were placed into
respective tared quartz sample holders at an initial ambient room humidity setting of
about 46%RH and 33%RH, respectively. For this study, an additional 75%RH set
point was used. For 2 full cycles, data collection took about 7 days at 25°C and

about 17 days at 40°C to complete. After completion of each 2 cycle study, the samples were maintained at the same RH as the initial ambient starting RH.

X-ray Powder Diffraction (XRPD) patterns were taken on a Scintag XDS 2000
5 θ/θ diffractometer operating with copper radiation at 45kV and 40 mA, using a Kevex
Psi Peltier-cooled silicon detector. Source slits of 2 and 4 mm, and detector slits of
0.5 and 0.3 mm were used for data collection. Form II samples were gently milled
using an agate mortar and pestle for approximately one minute, placed in a platinum
sample pan, and leveled using a glass microscope slide. Samples taken during or
10 post hygroscopicity testing were not milled due to the limited amount of sample
available. In each case, powder diffraction patterns were scanned from 2° to 42° 2 θ at
1°/minute. Calibration of the XDS 2000 was verified using Silicon powder.

For variable relative humidity experiments, the larger capacity DVS-2 Surface
15 Measurement Systems Dynamic Vapor Sorption analyzer was used. Using a flow rate
of 500cc/min, Form II was held at desired RH settings and sampled periodically for
XRPD analysis. Unmilled material was placed in the platinum sample pan and leveled
using a glass microscope slide prior to analysis using the above conditions.

20 Form II showed a slow but continual weight gain through about 60%RH of
approximately 4%, and above 60% relative humidity an additional 15 - 20% weight
gain was observed. In contrast, Form I showed an approximate weight gain of 1 -
2% through about 75%RH, plus an additional estimated 3.5% weight gain through
about 90%RH. Above 90%RH, a weight gain of about 30% was observed. Thus,
25 Form II would be considered hygroscopic, while Form I would be considered
hygroscopic above 75%RH.

Variable humidity x-ray powder diffraction showed, that, as the humidity is
increased there is an apparent decrease in crystallinity in Form II, and a significant
30 change in the XRPD pattern which is presumably due to the loss of ethanol. Whereas
Form I apparently retains its crystallinity until extremely high relative humidity is
reached, (i.e., >98%) at which point it loses crystallinity and becomes amorphous.

Based upon these results, Form I has superior physical properties for relative to Form II for use as a pharmaceutical composition.

EXAMPLE 4

Form II

A reactor is charged under nitrogen atmosphere with (-)-cis-1-methyl-4R-(2,4,6-trimethoxyphenyl)-3S-piperidinol and acetic anhydride. Boron trifluoride etherate is added at a constant rate while stirring and cooling the resulting solution to 8-20°C. After the addition is complete the resulting mixture is stirred at 20-30°C for 3-5 hours. The reaction mixture is cooled to 8-12°C and ice-water is added while stirring followed by addition of aqueous sodium hydroxide until pH 10-11 is attained. The mixture is extracted with ethyl acetate. The ethyl acetate extracts are pooled and concentrated under vacuum. The residue is taken up in methanol and water. Then sodium hydroxide (about 50% aqueous solution) is added. The reaction mixture is stirred at 20-30°C for 2-3 hours. The mixture is evaporated under reduced pressure at $\leq 80^\circ\text{C}$. The residue is cooled to 15-20°C and brought to pH 8.5-9.5 using concentrated hydrochloric acid. A solid precipitates, which is collected by filtration washed with demineralized water and dried under reduced pressure to give ((-)-cis-1-methyl-4-(3-acetyl-4,6-dimethoxy-2-hydroxy)phenyl-3-piperidinol).

((-)-cis-1-methyl-4-(3-acetyl-4,6-dimethoxy-2-hydroxy)phenyl-3-piperidinol) is then added portionwise to a stirred suspension of potassium tert. butoxide in dry N,N-dimethylformamide at such a rate that the temperature does not exceed 20°C. After the addition is complete the resulting mixture is stirred for one hour at $\leq 30^\circ\text{C}$. Methyl 2-chlorobenzoate is added at such a rate, that the temperature does not exceed 30°C. the resulting mixture is stirred at 20-30°C for 4-6 hours. Demineralized water is added, followed by concentrated hydrochloric acid until the pH of the mixture reaches 6-8. The mixture is extracted two times using chloroform. The chloroform extracts are pooled together and concentrated under reduced pressure.

After cooling the remaining oil to $\leq 40^\circ\text{C}$, concentrated hydrochloric acid is added. The mixture is then stirred at $\leq 40^\circ\text{C}$ for ≤ 2 hours or overnight is necessary. After cooling the reaction mixture to 15-30°C, water and chloroform are added. The

resulting mixture is basified to pH 8.5-10.5 using sodium hydroxide solution (50%). The phases are separated. The aqueous layer is then extracted with chloroform. The combined organic extracts are evaporated under reduced pressure to yield (-)-cis-2-(2-Chlorophenyl)-5,7-dimethoxy-8-[4R-(3S-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-one as an oil, which is directly used in the next step without purification.

To (-)-cis-2-(2-Chlorophenyl)-5,7-dimethoxy-8-[4R-(3S-hydroxy-1-methyl)-piperidinyl]-4H-1-benzopyran-4-one, quinoline and pyridine hydrochloride are added. The resulting mixture is heated to 160-190°C while stirring. Stirring is continued while maintaining the temperature at 160-190°C for 2 hours. After cooling the reaction mixture to 90-110°C water is added. The resulting mixture is basified to pH 7.5-8.5 using saturated sodium carbonate solution. A mixture of ethanol twice with a mixture of ethanol and chloroform. The combined extracts are evaporated to dryness to obtain (+)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one crude as a brown gum, which is purified as follows.

To (+)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one crude, acetone is added. The resulting mixture is stirred at 55-60°C for 30-60 minute, then cooled to 15-20°C and stirred for another 1-2 hours. The precipitated solid is isolated by filtration, washed twice with acetone and dried under reduced pressure to give (+)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one in a purified form.

The free base from the previous step is suspended in ethanol and acidified using concentrated hydrochloric acid at such a rate that the temperature does not exceed 30°C. During this process initially all of the solid dissolves and then the hydrochloride precipitates. The suspension is cooled to 0-10°C and stirred for 1 hour while maintaining the temperature. The crystals are isolated by filtration and washed with cold ethanol to yield (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, crude.

To (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one hydrochloride, crude, ethanol is added. The resulting mixture is heated to 70-79°C, stirred for 1 hour while maintaining the temperature and then filtered while still hot. The filter is rinsed with hot ethanol. The filtrate is concentrated by atmospheric distillation, until 60-80% of the volatiles have been removed. The remaining suspension is then cooled to 0-10°C while isolated by filtration and dried under reduced pressure to give (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4-H-1-benzopyran-4-one hydrochloride, purified as a yellow solid.

After the Form I is recovered, a pharmaceutical composition can be prepared. As used herein, "pharmaceutical composition" means a therapeutically effective amount of Form I with a pharmaceutically acceptable carrier.

A "pharmaceutically acceptable carrier" is an agent which is non-toxic, does not interfere with the therapeutic profile of Form I and is appropriate to the method of administration. Form I is preferably administered by the intravenous route over an appropriate period of time for cancer chemotherapy. Preferably, Form I is mixed with one or more pharmaceutically acceptable carriers. For example, Form I may be mixed with iso-osmotic and pH controlled liquids such as water, dextrose/water or saline/water for injection intravenously into the patient.

An "effective amount" includes a "therapeutically effective amount", "an effective protein kinase inhibiting amount", "an effective cyclin dependent kinase amount" and an effective tumor-inhibiting amount of Form I and will vary with the individual, concomitant therapy, the disease, and other variable factors. An effective amount for Form I will be about the same as for Form II. Typically, the dosage of Form I will be 0.001mg/kg to 100 mg/kg per day.

Flavopiridol is useful in treating a number of conditions or diseases that benefit from inhibition of protein kinases, and more particularly cyclin dependent kinases as previously described herein. Flavopiridol is expected to be useful in treating a broad

range of cancers including, for example, leukemia, mesothelioma and cancers of the lung (large cell, small cell and non-small cell), colorectal, breast, ovarian, prostate melanoma, renal, uterine body and central nervous system.

5 All articles and patents cited herein are hereby incorporated herein by reference.

10

15

What is claimed is:

1. Pseudopolymorph Form I having an x-ray powder diffraction pattern expressed in terms of "D" spacing:

5

D space- A

10

12.708

4.323

5.594

5.349

3.590.

2. A pseudopolymorph Form I having an x-ray powder diffraction pattern expressed in terms of "D" spacing and relative intensities thereof:

15

D space- A

Relative Intensity

20

12.708

Strong

4.323

Strong

5.594

Strong

5.349

Medium

3.590

Medium

3.366

Medium

4.209

Medium

3.395

Medium

3.438

Medium

25

4.839

Medium.

3. A pseudopolymorph Form I having an x-ray powder diffraction pattern expressed in terms of "D" spacing and percentage of relative intensities thereof:

30

D space- A

Relative Intensity %

35

12.708

100.0

4.323

75.9

5.594

58.5

5.349

49.5

3.590

46.6

3.366

42.0

4.209

40.7

3.395

39.5

3.438

38.8

40

4.839

37.1.

4. A pseudopolymorph Form I having an x-ray powder diffraction pattern as defined in Table 1:

Table 1

2 Theta Angle (°)	D Space - Å	Relative Intensity	Relative Intensity (%)
6.950	12.708	Strong	100.0
20.529	4.323	Strong	75.9
15.830	5.594	Strong	58.5
16.560	5.349	Medium	49.5
24.778	3.590	Medium	46.6
26.457	3.366	Medium	42.0
21.091	4.209	Medium	40.7
26.226	3.395	Medium	39.5
25.898	3.438	Medium	38.8
18.320	4.839	Medium	37.1
8.308	10.634	Medium	35.7
23.748	3.744	Medium	33.4
13.010	6.799	Medium	32.4
30.520	2.927	Medium	31.0
27.106	3.287	Weak	26.2
31.153	2.869	Weak	22.4
29.043	3.072	Weak	23.7
14.600	6.062	Weak	22.4
19.033	4.659	Weak	20.6

5. The Form I of claims 1, 2, 3 or 4 wherein the Form I is essentially free of Form II.

6. The Form I of claims 1, 2, 3 or 4 wherein the Form I is essentially free of Form II and other Forms of Flavopiridol.

7. The Form I of claims 1, 2, 3 or 4 wherein Form II and other forms of Flavopiridol are present in less than 4%.

8. A pharmaceutical composition comprising a therapeutically effective amount of Form I of claim 1, 2, 3 or 4 and a pharmaceutical acceptable carrier.

9. A pharmaceutical composition comprising a therapeutically effective amount of the Form I of claim 1,2,3 or 4, which is essentially free of Form II, and a pharmaceutical acceptable carrier.

5 10. A pharmaceutical composition comprising a therapeutically effective amount of the Form I of claim 1,2,3 or 4, which is essentially free of Form II and other forms of Flavopiridol, and a pharmaceutical acceptable carrier.

10 11. A method of treating a patient for cancer by administering to the patient a therapeutically effective amount of Form I of claim 1, 2, 3 or 4.

12. The method of claim 11 wherein the Form I is essentially free from Form II or other Flavopiridol forms.

15 13. A method of inhibiting protein kinases in a patient by administering to the patient in need thereof an effective protein kinase inhibiting amount of the Form I of claims 1, 2, 3 or 4.

20 14. The method of claim 13 wherein the Form I is essentially free from Form II or other forms of Flavopiridol.

25 15. A method of inhibiting cyclin dependent kinases in a patient by administering to the patient in need thereof an effective cyclin dependent kinase inhibiting amount of Form I of claims 1, 2, 3 or 4.

16. The method of claim 15 wherein the Form I is essentially free from Form II or other forms of Flavopiridol.

17. A method of making the Form I of claims 1, 2,3 or 4 comprising

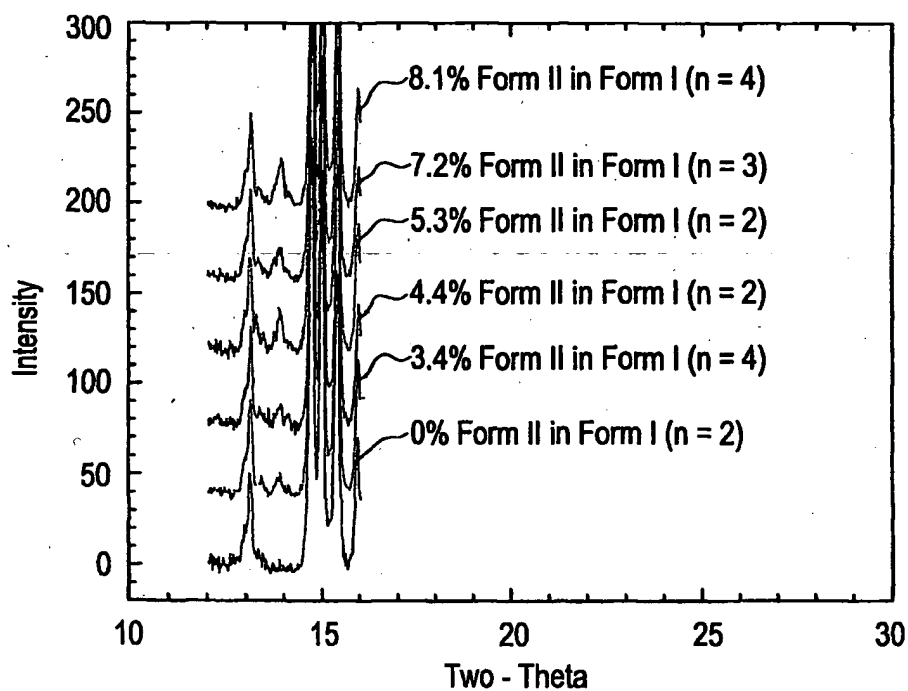
- 30 (a) combining a sufficient quantity of Form II with a sufficient amount of an appropriate azeotropic solvent, thus forming an azeotropic mixture;
- (b) submitting the azeotropic mixture to azeotropic distillation sufficient to form Form I; and
- (c) optionally recovering Form I therefrom.

18. The method of claim 17 wherein the solvent is a ketone solvent.
19. The method of claim 17 wherein the solvent is methyl ethyl ketone.
- 5 20. The method of claim 15 wherein the crystallized Form I is recovered by filtering Form I.
- 10 21. The method of claim 15 wherein the temperature of the azeotropic distillation is about 73 °C to about 80 °C.
- 15 22. A form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one or one of its pharmaceutically acceptable salts characterized by a weight gain due to water of less than five percent at a relative humidity of about 75%.
- 20 23. A form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride characterized by a weight gain due to water of less than five percent at a relative humidity of about 75%.
- 25 24. The Form I of claims 1, 2, 3 or 4 for use as a pharmaceutically active compound.

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FIG. 1

Estimated Detection Limit
HMR 1275 Form II in Form I Bulk Drug Substance



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/00519

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/04 A61K31/435 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 284 856 A (NAIK RAMCHANDRA G ET AL) 8 February 1994 (1994-02-08) cited in the application column 8, line 51; example 9	1-24
X	LI, PING ET AL: "Evaluation of intravenous flavopiridol formulations" PDA J. PHARM. SCI. TECHNOL. (1999), 53(3), 137-140 , XP000995938 figures 1,2	1-24
A	SEDLACEK ET AL.: "Flavopiridol, a new kinase inhibitor for tumor therapy" INT. J. ONCOLOGY, vol. 9, pages 1143-1168, XP002103774 cited in the application the whole document	1-24

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/US 01/00519

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